ASBMT
American Society for Blood and Marrow Transplantation

Innovative Supportive Care Practices for Stem Cell Transplantation in India

Mammen Chandy

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) may be considered as an inappropriate technology in a developing country because of the high cost of the procedure for an individual patient [1]. To make this modality available to a larger population as a life-saving treatment, innovations and modifications are required to reduce the cost without compromising the outcomes. This article describes our attempts to develop a cost-effective HSCT program in India [2].

Transplant Unit

The HSCT program at Christian Medical College (CMC), Vellore, was started in 1986, and up to December 2007, approximately 700 transplants have been performed, the majority from matched family donors.

In January 2008 a new transplant unit with 10 positive-pressure HEPA-filtered rooms for allogeneic transplants and 8 rooms for autologous transplants with all support facilities and a floor area of 1500 square meters was completed at a total cost of $750,000. Because infection control is of utmost importance in developing countries, surveillance microbiology for air quality is done once a month with blood agar plates for bacterial counts and Sabouraud's dextrose agar for fungi. Water for the patient's toilet needs and for cleaning the unit is UV sterilized and terminally filtered with a 0.2-micron shower head filter (Pall AQL3).

Unrelated Donor Registry in India

The matched unrelated donor transplant field is far lagging behind because of a lack of a formal nationalized unrelated donor registry program in India. The Asian Indian Marrow Donor Registry (AIMDR) is located in New Delhi, with a database of only 3000 registered donors. Few private cord blood banks exist, but the utilization of the units has been minimal.

Conditioning Regimens

Currently, only well-tried out regimens are being used because of a higher cost of new drugs. Reduced-intensity conditioning (RIC) regimens are increasingly being preferred for acute leukemias and aplastic anemia (AA), in view of decreased toxicity and less supportive care needs.

The following conditioning regimes are in use:

1. Thalassemia: busulfan (Bu), cyclophosphamide (Cy) ± antithymocyte globulin (ATG);
2. Acute myelogenous leukemia (AML): Bu 16 + Cy 120 was the standard regimen; more recently, RIC with fludarabine (Fl) and melphalan (Mel) has been preferred. For relapsed/refractory AML, if there is an HLA matched sibling donor available, it may be more cost effective to combine reinduction with FLAG-Ida followed by allogeneic stem cell rescue (avoiding the cost and toxicity of preparative regimen), but this approach is being evaluated in a larger number of patients [3,4];
3. Acute lymphoblastic leukemia (ALL): standard fractionated total body irradiation (TBI) (1200 cGy) and Cy 120 mg/kg;
4. Severe AA (SAA): fludarabine (Flu; 180 mg/m^2) and Cy (120 mg/kg) is the preferred regimen, and ATG (ATGAM, 40 mg/kg) is added only if the patient does not harbor any major infection at the time of transplant and has adequate financial resources [5].

In the developing world, the choice of conditioning regimen is critical, because rejection, treatment-related morbidity, and graft-versus-host disease (GVHD) will significantly increase the cost of the procedure.

Bone Marrow Harvest

Bone marrow is still the preferred graft source for thalassemia at our center, because peripheral blood stem cells (PBSCs) carry a higher risk of chronic

From the Hematology Department, Christian Medical College, Vellore 632004, TN, India.
Financial disclosure: See Acknowledgments on page 98.
Correspondence and reprint requests: Mammen Chandy, MD, Hematology Department, Christian Medical College, Vellore 632004, TN, India (e-mail: mammen@cmcvellore.ac.in).
1083-8791/09/151S-0001$36.00/0
doi:10.1016/j.bbmt.2008.10.021

GVHD (cGVHD) for nonmalignant disorders. The harvest is done using sternal aspiration needles, and this is associated with much less postharvest pain. The marrow is put into a collection system fabricated in-house with a 1-liter sterile bag docked to a 170-μ filter. For major ABO mismatched transplants, red cell depletion is done using hydroxyethyl starch and gravity sedimentation. For leukemia, PBSCs are collected using a Cobe Spectra after administration of granulocyte colony-stimulating factor (G-CSF) to the donor.

GVHD Prophylaxis

Short-course methotrexate (MTX) and cyclosporine (CsA) are still the main agents used, but we are exploring other regimes without MTX, particularly where earlier engraftment will significantly reduce transplant-related morbidity, for example, patients with SAA who have infection at the time of transplant, and in patients with Lucarelli Class III thalassemia where sinusoidal obstruction syndrome (SOS) is a major problem [6]. GVHD is treated with steroids and additional agents as required. Monoclonal antibodies (mAbs) are used only in those situations where there are no financial constraints. We are also studying the use of third-party mesenchymal cells (MSC) in steroid refractory GVHD. The MSC are produced in-house from third-party bone marrow in a GMP facility and are released only after meeting stringent criteria. This is a Department of Biotechnology, Government of India funded trial, and hence, accurate cost is not available at present.

Blood Products

All cellular blood products are irradiated with a blood irradiator indigenously manufactured by the Atomic Energy Commission of India at one-third the cost of irradiators available in the West. Packed red cell transfusions are given to maintain Hb >9 g% and platelet transfusion to maintain platelet counts around 20,000/cumm. We insist on 1 or 2 relative donors being available in the peritransplant period to provide single-donor platelets.

Leukodepletion filters are not routinely used because this will increase the total transplant cost by 10% to 15%, even though most patients and donors are cytomegalovirus (CMV) IgG positive.

Incidence of hepatitis in pretransfused thalassemia patients has been analyzed. Five of 243 (2.05%) patients were HBs Ag positive and 31 of 243 (12.75%) were HCV Ab positive prior to HSCT. Lamuvidine is given to HBs Ag-positive patients pre-transplant, and booster doses of hepatitis B vaccination are given to the patient and donor if the HBSAb titer is less than 100 IU. The outcomes of HSCT for HBs Ag-positive patients has not been adversely affected using this strategy. The hepatitis C positivity also does not affect the HSCT outcomes provided the liver function tests are within normal limits. PEG interferon and Ribavarine is used posttransplant if the patient remains HCV postitive once the serum ferritin levels return to normal, to prevent viral replication. Although this adds to the cost of HSCT, there is no choice if the patient remains HCV positive.

Chimerism

We have developed an algorithm of STR/VNTR markers for evaluation of chimerism posttransplant, with quantification being done using gene scan. The cost of this indigenous chimerism analysis is US$ 50. Testing is done at day +30 and only if there is mixed chimerism testing is repeated at a frequency depending on the clinical situation [7].

Infection Management

No prophylactic antimicrobials are administered pretransplant. Acyclovir is started on day +1 to prevent herpes simplex, but fluconazole is not given prophylactically. Gram-negative sepsis is more frequent than Gram-positive infections and recently pan-resistant nosocomial infection is becoming a problem. If fever persists >72 hours, conventional amphotericin desoxycholate is administered as a 4-hour infusion. If there is CT evidence of fungal infection then Voriconazole or caspofungin is added. A generic liposomal amphotericin preparation (Fungizome), which is one-fifth the cost of Ambisome is used when there is infusional toxicity with amphotericin desoxycholate [8].

All patients transplanted and their donors so far have been CMV IgG positive. Posttransplant CMV-polymerase chain reaction (PCR) is done on day +30, and if negative, repeated only if there is clinical suspicion of CMV or if the patient has developed GVHD requiring immunosuppression. Pre-emptive treatment with ganciclovir is started if a negative CMV-PCR becomes positive or there is a rising titer [9].

Intravenous immunoglobulin at a dose of 400 mg/kg every 4 weeks is given as prophylaxis in a few patients where there are no resource constraints. Once engraftment has occurred, cotrimoxazole and oral penicillin are started and continued for 1 year posttransplant.

Using the above-mentioned strategy for the CMV monitoring and without the use of leukodepletion filters for transfusions, the incidence of CMV reactivation is 38.8% and CMV disease has been documented in 23.1% patients; the majority of these patients were on increased immunosuppression for GVHD. Therefore, more active CMV monitoring is currently being advocated for patients with GVHD.

No prophylaxis is given for tuberculosis or malaria because there would be too many drug interactions in the posttransplant period, and these infections can be diagnosed and treated as and when necessary [10].

Table 1. Allogeneic transplants: October 1986 to December 2007

Diagnosis	N	Overall Survival%
Thalassemia major	242	71
Chronic myeloid leukemia	99	44
Acute myeloid leukemia	132	36
Aplastic anemia	102	61
Acute lymphoblastic leukemia	44	30
MDS	32	41
Multiple myeloma	3	100
PNH	6	67
Myelofibrosis	5	60
Fanconi anemia	8	50

MDS indicates myelodysplastic syndrome; PNH, paroxysmal nocturnal hemoglobinuria.

Nutrition

All food given to the patient is prepared by the relatives who pressure cook the food in a pantry adjacent to the transplant unit; this keeps the relatives busy, decreases the cost to the hospital, and the patient gets the type of food that he is used to having at home. Total parenteral nutrition (TPN) is started when the oral intake is poor, using commercial products at a cost of $30 per day for 2000 calories. Lipid is used only if long-term nutritional support is required for patients with gut GVHD. An ELD 96 (Pall) filter is used on the TPN line and this is changed every fourth day.

Most families rent an apartment for $30 per month where they cook their own food and stay until the patient is discharged and ready to go home. Patients generally stay in-house until they are totally free of complications, because the supportive care available in their home town may not be adequate. Therefore, average length of stay cannot be used as a variable for comparisons with other transplant programs.

Results of HSCT

In the transplant program started in 1986 and up to December 2007, a total of 718 allogeneic transplants have been performed in 683 patients. Table 1 gives the indications for transplant and the outcomes. The median age of patients was 16 years (range: 5 months to 64 years) with 67.8% of the patients being males. The age distribution is shown in Figure 1, with half of the transplants being done in children. Table 2 gives the results of bone marrow transplantation (BMT) for thalassemia, and the outcome in Class II is similar to that reported from Pesaro, India [11]. RIC with Flu and Mel for AML is associated with much lower treatment-related mortality (TRM), and, therefore, a lower cost, and short-term overall survival (OS) appears to be better than ablative conditioning with Bu and Cy [3]. For SAA, conditioning with Flu and Cy has reduced rejection with better survival: we do not wait for resolution of fevers before starting conditioning in severely neutropenic patients.

Table 2. Outcome of Allogeneic BMT for Thalassemia 1986-2007

Class	Number	Survival (%)	Event-Free Survival (%)	Rejection (%)	Mortality (%)
All patients	218	159 (72.9)	142 (64.7)	32 (14.1)	59 (27.1)
Class I	15	11 (73.3)	11(73.3)	0	4 (26.7)
Class II	78	66 (84.6)	63 (80.8)	8 (10.3)	12 (15.4)
Class III	125	82 (65.6)	67 (53.6)	24 (19.4)	43 (34.4)

BMT indicates bone marrow transplantation.

Cost

Figure 2 shows the cost distribution for BMT at CMC, Vellore. The total cost of HSCT ranges from $20,000 to $75,000, depending upon the type of donor and complications representative cost of BMT in patients with thalassemia, leukemia and aplastic anemia depending on the presence or absence of complications is shown in Table 3.

The first matched unrelated SCT for a 45-year-old male with AML in the second complete remission (CR2) was recently done at this center, with stem cells procured through the National Marrow Donor Program (NMDP) from a donor in Florida: the cost of high-resolution typing of patient and donors, collection of stem cells, and carriage to India was US$ 40,000, and the transplant cost in India was only US$ 30,000. Therefore, it is logical to develop a matched unrelated transplant program locally, with the graft sourced from anywhere in the world and patients traveling here for HSCT at a much reduced cost.

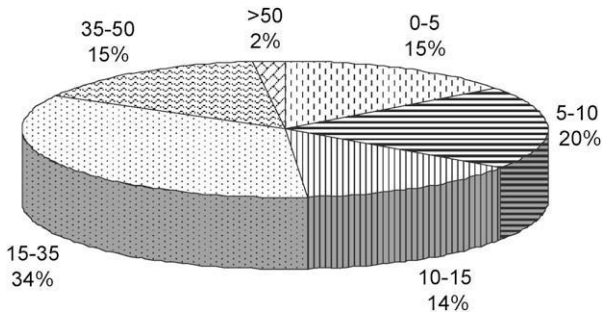

Figure 1. Age distribution of patients transplanted 1986-2007.

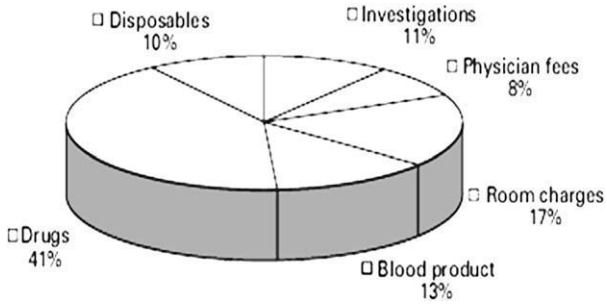

Figure 2. Alogeneic BMT—cost distribution 2007.

Table 3. Representative Cost of Transplant in Individual Patients

Diagnosis	UPN	Age	BSAm2	Hospital Stay (Days)	Cost of Transplant in US$
Aplastic anemia uncomplicated	458	29	1.67	28	14,000
Aplastic anemia complicated	701	46	1.59	145	72,000
Thalassemia uncomplicated	731	4	0.62	46	14,000
Thalassemia complicated	707	10	1.0	51	22,000
Acute leukemia uncomplicated	697	38	1.5	31	11,000
Acute leukemia complicated	672	17	1.64	146	57,000

In conclusion, it is possible to develop a cost-effective allogeneic stem cell transplant program in the developing world that will provide the patient a life-saving treatment at an affordable cost in his own country. Development of indigenous technology, cost-effective drug intervention, and monitoring strategies and continuous analysis of outcomes are important factors in developing such a program.

ACKNOWLEDGMENTS

Financial disclosure: The author has nothing to disclose.

Consultants: Dr. Alok Srivastava, Dr. Vikram Mathews, Dr. Biju George, Dr. Auro Vishwabandya, Registrars, Nurses, and Technicians in the Hematology Department.

REFERENCES

1. Dennison D, Vaughan WP, Chandy M, et al. Bone marrow transplantation in India: appropriate or inappropriate technology? *Int Third World Stud J Rev*. 1990;2:1-5.
2. Chandy M, Srivastava A, Dennison D, Mathews V, George B. Allogeneic bone marrow transplantation in the developing world: experience from a center in India. *Bone Marrow Transplant*. 1999;27:785-790.
3. Chandy M, Mathews V, Rajasekar T, et al. Fludarabine and melphalan conditioning regimen in young patients with acute myeloid leukemia in CR1 undergoing a matched related allogeneic stem cell transplant: a single center experience. ASH Annual Meeting Abstracts. *Blood*. 2007;110:5049.
4. Chandy M, Mathews V, Rajasekar T, et al. Treatment of relapsed and refractory acute myeloid leukemia with a salvage FLAG-IDA chemotherapy regimen followed by a HLA matched related allogeneic PBSC infusion without additional conditioning. ASH Annual Meeting Abstracts. *Blood*. 2007;110:5050.
5. George B, Mathews V, Viswabandya A, Kavitha ML, Srivastava A, Chandy M. Fludarabine and cyclophosphamide based reduced intensity conditioning (RIC) regimens reduce rejection and improve outcome in Indian patients undergoing allogeneic stem cell transplantation for severe aplastic anemia. *Bone Marrow Transplantat*. 2007;40:13-18.
6. George B, Mathews V, Viswabandhya A, Kavitha ML, Srivastava A, Chandy M. Acute and chronic graft-versus-host disease (GVHD) in patients undergoing allogeneic BMT for thalassaemia major. *Biol Blood Marrow Transplant*. 2005;11:9-10.
7. Sellathamby S, Balasubramanian P, Sivalingam S, et al. Developing an algorithm of informative markers for evaluation of chimerism after allogeneic bone marrow transplantation. *Bone Marrow Transpla*. 2006;37:751-755.
8. George B, Mathews V, Srivastava A, Chandy M. Infections among allogeneic bone marrow transplant recipients in India. *Bone Marrow Transplant*. 2004;33:311-315.
9. Finny GJ, Mathews V, Abraham P, et al. A pilot study on the role of cytomegalovirus & human herpesvirus-6 infections in Indian bone marrow transplant recipients. *Indian J Med Res*. 2001;114:39-46.
10. George B, Mathews V, Srivastava V, Srivastava A, Chandy M. Tuberculosis among allogeneic bone marrow transplant recipients in India. *Bone Marrow Transplantat*. 2001;27:973-975.
11. Chandy M, Mathews V, Kavitha ML, Viswabandya A, George B, Srivastava A. Bone marrow transplantation for β thalassemia major: long term experience from a single centre in India. ASH Annual Meeting Abstracts. *Blood*. 2007;110:1106.